Original Article / Özgün Makale

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1168976

J Med Palliat Care 2022; 3(3): 280-287

Role of neutrophil-to-lymphocyte, mean platelet volume-to-platelet and platelet-to-lymphocyte ratios as predictors of disease severity in Rotavirus gastroenteritis

Rotavirüs gastroenteritinin şiddetin belirlenmesinde nötrofil lenfosit, ortamala trombosit hacmi trombosit ve trombosit lenfosit oranlarının rolü

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Cite this article as/Bu makaleye atıf için: Güven D, Sarıcı D. Role of neutrophil-to-lymphocyte, mean platelet volume-to-platelet and platelet-to-lymphocyte ratios as predictors of disease severity in Rotavirus gastroenteritis. J Med Palliat Care 2022; 3(3): 280-287.

ABSTRACT

Aim: In developing countries, Rotavirus Gastroenteritis (RG) is even now one of the most common causes of death and morbidity. As a result, clinicians must be extremely vigilant in detecting the presence and severity of RG. The goal of this study was to identify predictors of RG severity by analyzing complete blood counts, including neutrophil-to-lymphocyte ratio (NLR), mean platelet volume-to-platelet volume (MPV/P); platelet-to-lymphocyte ratio (PLR).

Material and Method: Data were obtained retrospectively from medical records of 456 children diagnosed with RG and age-matched healthy children from University of Health and Sciences, Ankara Atatürk Sanatorium Training and Research Hospital between January 2019 and December 2021. The Vesikari Score was used to categorize disease severity as severe or mild. Variables' prognostic effects on disease severity were equated across groups.

Results: The study included 456 children with RG. Two hundred thirty two of them were severe; 126 males; median age: 1.24 (0.41-2.36 years), 224 of them non-severe; 126 males; median age 1.52 (1.01-2.84 years). The median length of hospitalization was 5 (4-7) days for the severe group and 2 (0-3) days for the non-severe group ($p<0.001$). Neutrophils, monocyte, platelet, red cell distribution width, NLR, and PLR levels in RG patients were statistically significantly higher than in the control group, while hemoglobin, platelet distribution width, MPV, and MPV/P levels were lower ($p<0.001$). The area under the operating characteristic curve (AUC) for NLR, and MPV/P for severe disease was calculated as (0.556; and 0.709, respectively), and was all statistically significant ($p<0.001$). However, PLR was not found statistically significant in ROC analysis ($p>0.001$).

Conclusion: NLR was increased and MPV/P was decreased with the increase in severity of Rotavirus Gastroenteritis. NLR and MPV/P were useful for providing additional severity stratification in RG.

Keywords: Rotavirus, children, severity, neutrophil-to-lymphocyte ratio, mean platelet volume-to -platelet volume, platelet-to-lymphocyte ratio

ÖZ

Amaç: Gelişmekte olan ülkelerde Rotavirus gastroenteriti (RG) günümüzde bile en yaygın ölüm ve morbidite nedenlerinden biridir. Sonuç olarak, klinisyenler RG'nin varlığını ve ciddiyetini tespit etmede son derece uyanık olmalıdır. Bu çalışmanın amacı, nötrofil lenfosit oranı (NLO), ortalama trombosit hacmi trombosit oranı (OTH/T) ve trombosit lenfosit oranı (TLO) dahil olmak üzere tam kan sayımlarını analiz ederek RG şiddetinin öngörücülerini belirlemekti.

Gereç ve Yöntem: Veriler, Ocak 2019 ile Aralık 2021 tarihleri arasında Sağlık Bilimleri Üniversitesi, Ankara Atatürk Sanatoryum Eğitim ve Araştırma Hastanesinde de RG tanısı konan 456 çocuğun tıbbi kayıtlarından ve aynı yaştaki sağlıklı çocukların tıbbi kayıtlarından geriye dönük olarak elde edildi. Hastalık şiddetini; şiddetli veya hafif kategorize etmek için Vesikari skoru kullanıldı. Değişkenlerin hastalık şiddeti üzerindeki prognostik etkileri gruplar arasında karşılaştırıldı.

Bulgular: Çalışmaya RG'lı 456 çocuk dahil edildi. Bunlardan iki yüz otuz ikisi şiddetliydi; 126 erkek; medyan yaş: 1,24 (0,41-2,36) yıl, 224'ü şiddetli değil; 126 erkek; medyan yaş 1,52 (1,01-2,84) yıldı. Hastanede medyan kalış süresi ağır grup için 5 (4-7) gün ve ağır olmayan grup için 2 (0-3) gündü ($p<0,001$). RG hastalarında nötrofil, monosit, trombosit, eritrosit dağılım genişliği, NLO ve TLO düzeyleri kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksek, hemoglobin, trombosit dağılım genişliği, OTH ve OTH/T düzeyleri ise daha düşüktü ($p<0,001$). ROC analizinde; NLO ve OTH/T için operasyon karakteristik eğrisi (AUC) altında kalan alan, şiddetli hastalık için (sırasıyla 0,556 ve 0,709) olarak hesaplandı ve tümü istatistiksel olarak anlamlıydı ($p<0,001$) fakat TLO istatistiksel olarak anlamlı bulunmadı ($p>0,001$).

Sonuç: Rotavirüs Gastroenteritinin şiddetinin artmasıyla NLO artmış ve OTH/T azalmıştır. NLO ve OTH/T, RG'de ek şiddet sınıflandırma sağlamak için faydalı bulunmuştur.

Anahtar Kelimeler: Rotavirüs, çocuklar, şiddet, nötrofil lenfosit oranı, ortalama trombosit hacmi-trombosit oranı, trombosit lenfosit oranı

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Received/Geliş: 31.08.2022 **Accepted/Kabul:** 22.09.2022

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INTRODUCTION

Rotavirus is a double-stranded RNA virus. Although humans of all ages can become infected with rotavirus, children aged 3 to 24 months account for the majority of severe infections. The most common reason of serious gastroenteritis in children below the age of five is rotavirus. Rotavirus was responsible for 25 million doctor visits, two million hospital stays, and nearly 400 000 deaths among children under the age of five worldwide (1). Rotavirus can cause viremia despite the fact that it frequently infiltrates the surface epithelium of the small bowel villi, causing local inflammation. Rotavirus can also cause pneumonia, disseminated intravascular coagulation, nephritis, exanthema, elevated transaminase, hemophagocytic lymphohistiocytosis, and neurological manifestations (2-7).

Neutrophils, lymphocytes, platelets and red blood cells (RBC) are important cell types that are counted in a complete blood count (CBC). Red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV) and mean platelet volume-to-platelet ratio (MPV/P), platelet distribution width (PDW) are newly defined inflammatory markers from these CBC parameters. The levels of these inflammatory markers have been linked to the severity of a variety of diseases (8-13).

As a result, NLR, PLR, and MPV/P ratios were thought to be indicators of disease severity, based on changes in all CBC parameters due to rotavirus viral pathogenicity in RG. Early detection of severe RG is critical for initiating supportive treatment on time, identifying complications as soon as possible, and referring patients to appropriate centers. We wanted to investigate the relationship of CBC parameters and ratios such as NLR, MPV/P, and PLR with disease severity, so we analyzed the clinical and laboratory characteristics of 456 patients with RG to determine the predictors of severe disease.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health and Sciences, Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (Date: 12.10.2021, Decision No: 2012-KAEK-15/2388). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. With the ethics committee approval, the data were scanned retrospectively using the Hospital Information Management System.

A retrospective, cross-sectional study included children diagnosed with RG at pediatric clinics between January 2019 and December 2021, as well as age-matched healthy children. Healthy children were chosen only those being brought in for regular checks. Children with hematologic, inflammatory, or chronic disease, and also those with a positive microscopy test for parasites and/or bacteria in culture specimens, were not included in the study. Rotavirus antigen test were on all children who had gastroenteritis. The severity of diarrhea in children with gastroenteritis was evaluated utilizing 20-point Vesikari Risk Score (14). After that, we divided the children into groups depending on their Vesikari scores: non-severe <11 or severe ≥11. Demographic characteristics, whole blood count, and other biochemical test results of all children included in the study were evaluated on presentation. The LH-780 system was used for CBC analysis (Beckman Coulter Diagnostics, Image 8000, Brea, CA). The highly sensitive and specific ELISA test was used to detect rotavirus in fresh stool samples (Rota Adeno Antigen Test Device, Cambridge). A standard biochemical analyzer was used to examine serum biochemistry samples (Hitachi 902 Automatic Analyzer, Roche Diagnostics, Germany).

Statistical Analysis

SPSS for Windows, version 22.0, was used to analyze the data (SPSS Inc., Chicago, IL, United States). The Kolmogorov Smirnov test was used to determine whether the distribution of continuous variables was normal or not. The Levene test was used to assess variance homogeneity. For skewed distributions, continuous data were described as median (interquartile range: third quartile - first quartile) unless otherwise specified. The number of cases was used to describe categorical data (percent). The Mann Whitney U test was used to compare differences in not normally distributed variables between two independent groups. The Kruskal-Wallis test was used to compare differences in not normally distributed variables between three independent groups. The Conover-Inman test was used to compare binary comparisons between groups, and the p value was set at < 0.05. Pearson's chi-square test or Fisher's exact test were used to compare categorical variables. The cut off values of the NLR, MPV/P, and PLR associated with the risk of severity were determined using ROC curve analysis. In all statistical analyses, the p-value of < 0.05 was accepted as the significance level.

RESULTS

The study included 456 children with RG. Two hundred thirty two of them were severe; 126 males; median age: 1.24(0.41-2.36 years), 224 of them non-severe; 126 males; median age 1.52 (1.01-2.84) years and 300 healthy controls; 140 males; median age: 1.39(0.75-2.52) years. The groups were well-matched in terms of mean age and gender ($p>0.05$) (**Table 1**).

Table 1. Demographic, and clinical, characteristics of the patients with Rotavirus Gastroenteritis and Controls

	RPAG (n=456) Vesikari Score		Healthy Controls (n:300)	p
	Severe (n:232)	Non-severe (n:224)		
Gender				>0.05
Male	126 (54.3%)	126 (56.3%)	140 (46.7%)	
Female	106 (45.7%)	98 (43.8%)	160 (53.3%)	
Age (Years)	1.24 (0.41-2.36)	1.52 (1.01-2.84)	1.39 (0.75-2.52)	>0.05
Hospitalization length (days)	5 (4-7)	2 (0-3)		<0.001
Intravenous hydration requirement	232 (100%)	153 (68.3%)		<0.001
Diarrhea	232 (100%)	224 (100%)		-
Vomiting	178 (76.7%)	158 (70%)		0.134
Fever	94 (40.5%)	20 (8.9%)		<0.001
Upper respiratory tract infection	18 (7.8%)	6 (2.7%)		0.015
Pneumonia	67 (28.9%)	3 (1.3%)		<0.001
Febrile seizure	14 (6%)	-		<0.001
Otitis media	3 (1.3%)	-		0.249
Skin rash	3 (1.3%)	-		0.249
Lymphadenitis	9 (3.9%)	-		0.004

Continuous variables are expressed as the median (Q1-Q3) and categorical variables are expressed as either frequency (percentage). Continuous variables were compared with Mann-Whitney U test, and categorical variables were compared using Pearson's Chi-square test or Fisher Exact test. Statistically significant p-values are in bold.

The median length of hospitalization was 5 (4-7) days for severe group and 2 (0-3) days for the non-severe group (p<0.001). All patients need intra-venous hydration in the severe group, while 68.3% in the non-severe group (p<0.001). The duration of hospitalization and the need of intra-venous hydration were found to be statistically significantly higher in the severe group compared to the non-severe group (p<0.001) (**Table1**).

While 40.5% of the severe group patients had fever, it was 8.9% in the non-severe group (p<0.001). Upper respiratory tract infection was found in 7.8% of severe group while 2.7% in the non-severe group. Pneumonia was accompanying in 28.9% of severe group, 1.3% in non-severe group (p<0.001).

Febrile seizure was found in 6% of severe group, none of the patients had febrile seizure in non-severe group (p<0.001). Otitis media (1.3%), skin rash (1.3%) and lymphadenitis (3.9%) were the other accompanying findings in severe group. The presence of fever, upper respiratory tract infection, pneumonia, febrile seizure, and lymphadenitis was statistically higher in the severe group compared to the non-severe group (p<0.05) (**Table 1**).

Glucose, albumin, calcium, bicarbonate, lymphocytes, RBC, hemoglobin (HGB), platelets, MPV, MPV/P levels were statistically significantly lower; blood-urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), potassium, neutrophils, eosinophil, basophil, NLR and PLR levels were statistically significantly higher in the severe group compared to the non-severe group (p<0.001) (**Table 2**).

Creatinine, AST, alanine aminotransferase (ALT), leukocytes, monocytes, neutrophils, platelets, RDW, and NLR levels were statistically significantly higher; total protein, albumin, alkaline phosphatase (ALP), sodium, eosinophil, HGB, MPV, PDW and MPV/P levels were statistically significantly lower in both severe and non-severe groups compared to the control group (p<0.001) (**Table 2**).

A ROC curve analysis was used to determine the efficacy of various parameters predicting severe prognosis (**Figure 1**, **Figure 2**). In the ROC analysis, the area under the operation characteristic curve (AUC) for MPV, NLR, and MPV/P for severe disease was calculated as (0.701; 0.556; and 0.709, respectively), and was all statistically significant (p<0.05). AUC for PLR was 0.542 and not found statistically significant (p>0.098). The cut-off value for MPV was accepted as 8.19, the sensitivity was calculated as 73.3%, specificity 63.5%. The cut-off value for NLR was accepted as 2.36, sensitivity was calculated as 34.9%, and specificity 94%. The cut-off value for MPV/P was accepted as 0.027, sensitivity was calculated as 70.3%, and specificity 65.6% (**Table 3**).

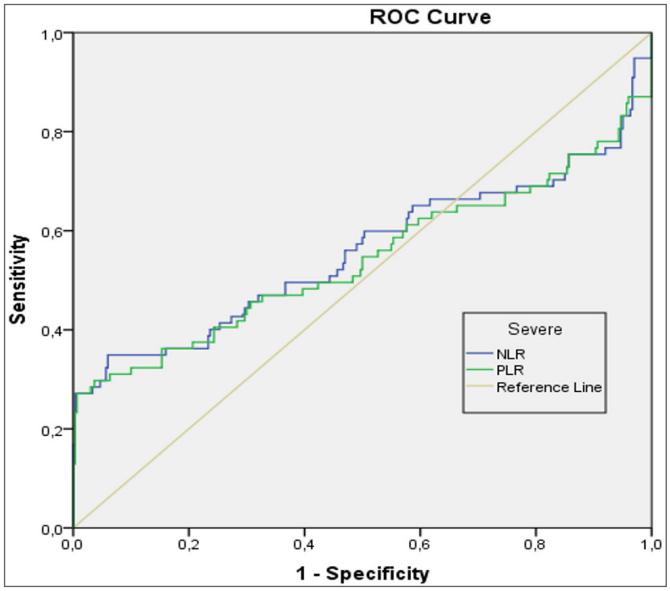

Figure 1. The ROC curves of NLR, PLR in predicting Rotavirus gastroenteritis

Table 2. Baseline blood-routine parameters of the patients with Rotavirus Gastroenteritis

	Severe (n:232)	Non-severe (n:224)	Healthy Control (n:300)	p
	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)	
CRP (mg/L)	1.99 (0.49-7.62)	2.22 (0.92-7.79)	-	0.238
Glucose (mg/dL)	82.91 (70.15-97.97)	84.15 (67.00-94.00)	86.24 (81.97-91)	0.023[a,b]
BUN (mg/dL)	23.50 (15.15-31.68)	18.81 (10.10-29.70)	17 (11.64-23)	<0.001[a,b]
Creatinin (mg/dL)	0.57 (0.41-0.55)	0.54 (0.40-0.48)	0.52 (0.48-0.59)	<0.001[a,b,c]
Total Protein(g/dL)	6.63 (6.16-7.00)	6.80 (6.26-7.13)	7.20 (7.00-7.5)	<0.001[b,c]
Albumin (g/dL)	4.20 (3.84-4.46)	4.40 (4.04-4.65)	4.55 (4.40-4.75)	<0.001[a,b,c]
AST (IU/L)	170.85 (36.48-231.83)	145.77 (72.83-216.91)	13 (10.78-16)	0.008[a,b,c]
ALT (IU/L)	29.25 (17.17-39.00)	24.88 (16.16-32.85)	22 (18.00-31)	0.001[b,c]
ALP (IU/L)	45.00 (36.00-54.54)	43.78 (36.36-53.5)	185.64 (133-219.5)	<0.001[b,c]
Calcium (mg/dL)	9.6 (9.3-10.21)	9.9 (9.60-10.3)	10.00 (9.60-10.4)	<0.001[a,b]
Sodium (mmol/L)	137.61 (135-139.59)	137.49 (135.6-140)	138.86 (137-140)	0.002[b,c]
Potassium (mmol/L)	4.33 (4.03-4.76)	4.11 (3.87-4.5)	4.34 (4.07-4.6)	<0.001[a,c]
Magnesium (mg/dL)	2.10 (2.00-2.22)	2.02 (1.92-2.25)	2.00 (1.90-2.2)	0.206
pH	7.33 (7.27-7.40)	7.35 (7.29-7.42)	-	0.026
Bicarbonate(mmol/L)	16.40 (13.46-19.80)	18.71 (15.3-21)	-	<0.001
Lactate	1.59 (1.30-2.18)	1.73 (1.20-2.02)	-	0.621
Leukocytes ($\times10^3$/μL)	9.43 (6.46-12.61)	9.29 (7.51-11.75)	7.10 (6.02-8.61)	<0.001[b,c]
Lymphocytes ($\times10^3$/μL)	2.26 (1.18-3.63))	2.94 (1.92-4.3)	2.87 (2.37-3.57)	<0.001[a,c]
Monocytes ($\times10^3$/μL)	0.84 (0.55-1.1)	0.71 (0.47-1.07)	0.46 (0.37-0.58)	<0.001[b,c]
Neutrophils ($\times10^3$/μL)	5.38 (3.41-8.25)	4.77 (2.85-6.68)	3.64 (2.60-4.69)	<0.001[a,b,c]
Eosinophil ($\times10^3$/μL)	0.04 (0.01-0.14)	0.02 (0.00-0.07)	0.16 (0.08-0.28)	<0.001[a,b,c]
Basophil ($\times10^3$/μL)	0.06 (0.02-0.11)	0.03 (0.02-0.07)	0.04 (0.02-0.06)	0.004[a,b]
RBC ($\times10^6$/μL)	4.55 (4.16-4.95)	4.76 (4.46-5.05)	4.89 (4.60-5.09)	<0.001[a,b]
Hemoglobin (g/dL)	11.92 (11.09-12.77)	12.44 (11.19-13.22)	13.45 (12.74-14.00)	<0.001[a,b,c]
HCT (%)	35.86 (33.33-37.62)	36.88 (33.60-39.55)	39.78 (37.64-41.98)	<0.001[a,b,c]
MCV (fL)	78.48 (47.82-82.97)	78.50 (74.82-81.80)	82.98 (80.00-87)	<0.001[b,c]
MCH (pg)	26.28 (25.17-28.21)	26.58 (24.30-27.61)	28.00 (27.00-29)	<0.001[b,c]
MCHC (g/dL)	33.66 (32.67-34.38)	33.46 (32.57-34.20)	33.60 (32.65-34)	0.320
Platelets ($\times10^3$/μL)	314.1 (242.2-410)	332.6(275.9-451.9)	293 (253.4-332.3)	<0.001[a,b,c]
MPV (fL)	7.52 (6.83-8.41)	8.09 (7.04-9.19)	8.93 (7.21-10)	<0.001[a,b,c]
PDW	15.80 (15.40-16.53)	15.84 (0.32-16.68)	16.19 (15.65-16.9)	<0.001[b,c]
RDW (%)	14.85 (13.55-16.45)	14.00 (13.85-15.95)	13.80 (13-15.19)	<0.001[b,c]
NLR	2.52 (0.98-4.89)	1.34 (0.74-3.35)	1.23 (0.84-1.81)	<0.001[a,b,c]
MPV/P	0.02 (0.01-0.03)	0.02 (0.02-0.04)	0.03 (0.02-0.04)	<0.001[a,b,c]
PLR	140.1 (95.24-236.6)	105.66(76.41-203.16)	102.6 (85.3-129.2)	<0.001[a,b]

Continuous variables are expressed as the median (Q1-Q3. Statistical analysis differences in not normally distributed variables between two independent groups were compared by Mann Whitney U test. Statistical analysis differences in not normally distributed variables between three independent groups were compared by Kruskal Wallis test. Statistically significant p-values are in bold. Conover-Inman test was performed for the binary comparisons among the groups and the p value was set at 0.05. Significant differences were found between; a: Severe vs non severe, b:Severe vs control group, c: Non severe vs control group. Abbreviations: CBC: Complete blood count; CRP: C-reactive protein; BUN: Blood Urea Nitrogen; ALT: Alanine aminotransferase ; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; RBC: Red Blood Cell: HCT: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin: MCHC: Mean Corpuscular Hemoglobin Concentration; MPV: Mean Platelet Volume, PDW: Platelet Distribution Width; RDW: Red Cell Distribution Width; NLR: Neutrophil-to-lymphocyte ratio; MPV/P: Mean platelet volume-to-platelet ratio; PLR: Platelet-to-lymphocyte ratio

Table 3. AUC, optimal cut-off, and sensitivity and specificity values of laboratory parameters

Test Result Variable(s)	AUC	Std. Error	p	95% CI	Cut Off	Sensitivity	Specificity
Severe							
MPV	0.701	0.022	<0.001	(0.657-0.745)	8.19	73.3%	63.5%
NLR	0.556	0.027	0.025	(0.503-0.610)	2.36	34.9%	94.0%
MPV/P	0.709	0.023	<0.001	(0.664-0.754)	0.027	70.3%	65.6%
PLR	0.542	0.027	0.098	(0.488-0.595)	-	-	-

AUC: Area under the ROC Curve. CI: Confidence interval

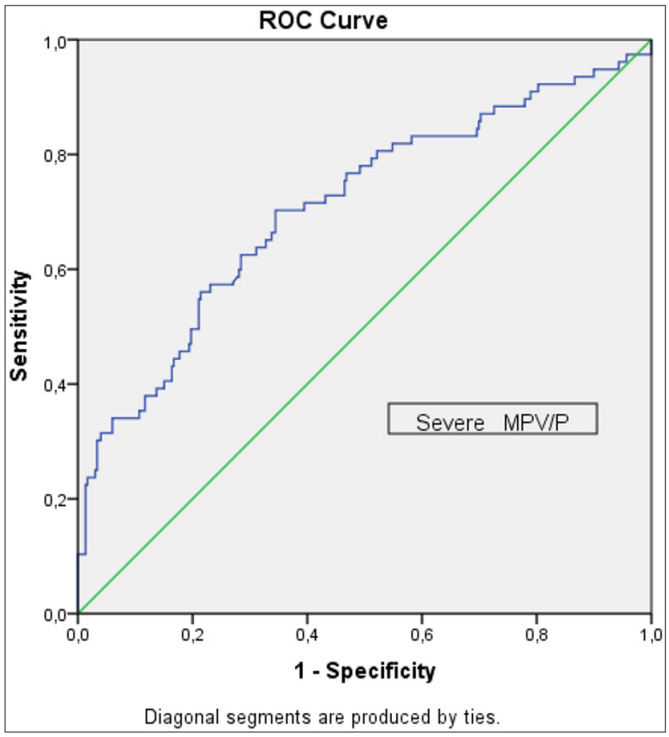

Figure 2. The ROC curve of MPV/P in predicting Rotavirus gastroenteritis

DISCUSSION

It has been reported that RG is more common under the age two and the preponderance of the disease was more in males (15,16). The reasons for the difference in detection rate between males and females are however, not known. The greater sensitivity of children aged below two years to the RG is thought to be due to their greater exposure to contaminated substances. Children in this age group are known to put all in their mouths, and the virus can survive on surfaces, including toys, thus they could become infected quite easily. Natural immunity has also been proposed as a possible explanation for the decrease in incidence with age. By age two, most children have been infected and are protected from subsequent symptomatic re-infection. The majority of children with for RG were under the age of two and in male gender in our study which is consistent with the literature (15,16). Age less than two years was significantly associated with increased diarrheal severity in terms of duration and frequency, as well as a higher modified Vesikari score, compared to age more than two years (15). However, in our study, no statistically significant difference was found for age between the severe and non-severe groups. Considering the older age of non-severe RG cases, children with diarrhea but in good general condition may have been followed at home by families and brought to the hospital less frequently. In addition, the clinician did not consider stool and blood tests necessary for mild cases, which may have caused these cases to be missed. Due to these reasons, the average age of the non-severe age group might have decreased, and there might not have been an age difference between the two groups.

In severe cases, the length of hospital stay was significantly longer and all of these patients required intravenous fluids as their dehydration worsened. Since the severity of the disease was determined based on diarrhea, vomiting duration, degree of dehydration, hospitalization and rehydration in the Vesikari Risk scoring system, it is expected that the length of hospital stay would be longer in severe cases.

There are numerous publications in the literature describing rotavirus infection systemic findings (2-7). Dehydration, electrolyte imbalance, upper respiratory tract infection, otitis media, pneumonia, febrile seizure, skin rash, malnutrition and lymphadenitis were systemic findings that associated with severe RG in our study. While 40.5% of the children in the severe group had high fever, 6% of them developed febrile convulsions due to high fever. Although the presence of pneumonia and rotavirus infection has been reported in previous studies, 28.9% rate in our study was remarkable. Rotavirus infection was not a nosocomial infection in any of these patients, and they were all evaluated at the time of their initial hospitalization.

BUN, creatinine, and blood gases (pH, serum bicarbonate) were discovered to be useful clinical markers to determine dehydration and severity in children with acute gastroenteritis (17-19). Higher levels of creatinine, BUN, potassium, and lower glucose, pH, bicarbonate, albumin levels in severe group were related to the serious dehydration and acidosis. Some studies have found a link between severe rotavirus diarrhea and hypocalcaemia (20). Although the calcium level was not found below the normal limits in RG patients, the calcium level was statistically lower in the children with RG infection compared to the control group, and in the severe group compared to the non-severe group. This could be due to the fact that NSP4-induced disruption of calcium homeostasis plays a critical role in the pathogenesis of diarrhea. It has also been suggested that rotavirus may cause seizures or make people more susceptible to them by altering calcium homeostasis through the same NSP4-induced changes (21).

RG was associated with transaminase elevation, as previously reported in other studies (22-24). Transaminase abnormalities could be caused by virus-induced liver damage, an immune response, or the creation and discharge of a metabolite or toxin during infection (25). Although AST and ALT levels increased in the severe group, only AST elevation was

found to be statistically significant and increased AST levels indicated disease severity, as previously reported (25,26).

Red cell distribution width (RDW) has been shown to rise during a variety of inflammatory events and pathophysiological conditions (8,27,28). Furthermore, numerous studies indicate that RDW can be used as diagnostic markers for disease severity (27,28). RDW and RG have only been studied once, and higher RDW levels were linked to severe rotavirus gastroenteritis (17). Severe and non-severe groups had significantly higher RDW levels than controls in our study however the increase in RDW was not associated with disease severity.

MPV and MPV/P have been identified as inflammatory and prognostic markers, with their role in inflammatory disorders previously demonstrated (9,29). Decreased MPV and increased MPV/P ratio have been found to be a predictor of clinical severity in a variety of diseases (9,29). MPV may rise in minimal inflammation due to the appearance of big platelets in the circulation, and after than MPV may lower with the inflammation severity because of the usage of these big platelets in the inflammation area (30). However, there are only a few studies on MPV's role in RG. MPV levels have been reported to be lower in RG (30,31). Furthermore, no difference in MPV levels was found between disease severity groups in these studies. We discovered that MPV levels were decreased in children with rotavirus gastroenteritis than in healthy controls, and that a decrease in MPV was a predictor for severe disease. There have been few studies on MPV/P and none on rotavirus gastroenteritis (9,29). In a study conducted in adult intensive care unit, patients who diagnosed with bacterial sepsis divided in into two groups as survival and non-survival for evaluating the severity of the sepsis. MPV/P ratio was found to be higher in non-survival patients compared to survival (9). Another study investigated the association between long-term mortality after myocardial infarction and the MPV and MPV/P. Relatively larger MPV with a low platelet count, as well as decreased MPV/P found to be predictor of long-term mortality (29). Low MPV/P, but not high MPV/P, was found to be associated with the presence of severe disease in our study. The reason for this could be that the studies in the literature were conducted on adults, one of them in bacterial sepsis and another in myocardial infection. In addition, these patients had lower platelet levels and higher MPV levels. Our patients had higher platelet levels but lower MPV levels, resulting in a lower MPV/P.

In this study, RG children had lower lymphocytes as well as higher neutrophils and monocytes than controls, and severe group children than non-severe. Neutrophils and lymphocytes are important components of the immune system and inflammatory response. Whereas a reduction in lymphocytes in blood plasma was already discovered in many infectious diseases, only a few studies support the link between rotavirus infection and a reduction in lymphocytes (32-34). In patients with rotavirus infection, a decrease in total lymphocytes is primarily caused by a marked reduce in T-cells. Virus infections can suppress the expression of important molecules required for T-cell survival, resulting in lower lymphocyte levels (33).

Rotavirus infection was reported to activate genes coding for chemokine's, and the inflammatory mediators were implicated in the chemo-taxis of neutrophils. Virus infections can cause neutrophils and monocytes to migrate to circulatory pools (33). Decreased lymphocytes as well as increased neutrophils resulted in a significant increase in NLR. It has been reported that NLR is a prognostic marker in many diseases and increasing NLR has a negative impact on disease prognosis (10,35). In our study, RG children had an elevated NLR levels than controls, and the severe group had a higher NLR levels than the non-severe group. There has only been one previous study (36) on the effect of NLR on rotavirus gastroenteritis, which supports our findings.

Patients with increased PDW value were linked to a more serious illness (11, 37). RG patients had lower PDW levels than controls in our study while we have not found that RDW was a predictor of the disease severity.

PLR is an inflammatory marker, and an increase in PLR levels indicates the severity of a variety of diseases (33,34). PLR was found to be increased in severe group than non-severe and controls in our study, but not statistically significant in ROC analysis.

Our study's limitation was that it was a retrospective, single-center study. To confirm this evidence, large-scale multicenter clinical trials are required.

CONCLUSION

Clinicians must be extremely vigilant in detecting the presence and severity of RG. NLR was increased and MPV/P was decreased with the increase in severity of RG. NLR and MPV/P were useful for providing additional severity stratification in RG and monitoring this severity predictors during treatment planning and following up on patients who are at a higher risk of progression, as well as lead a better understanding of the risk of complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health and Sciences, Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (Date: 12.10.2021, Decision No: 2012-KAEK-15/2388).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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